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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/144,838	08/31/1998	MICHAEL A. SIANI	GRFN-020/01U	5261

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EXAMINER	
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ART UNIT	PAPER NUMBER
1627	28

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Please find below and/or attached an Office communication concerning this application or proceeding.

file copy

Office Action Summary

Application No.	Applicant(s)
09/144,838	Siani et al.
Examiner	**Art Unit**
Bennett Celsa	1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 13, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *28-36* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *28-36* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Aug 31, 1998* is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 8/13/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/144,838 is acceptable and a CPA has been established. An action on the CPA follows.

Status of the Claims

Claims 28-36 are currently pending and under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

3. Applicant's election without traverse of native chemical ligation as the elected species in Paper No. 13 is again acknowledged.

Specification

4. The disclosure is objected to because of the following informalities: The preliminary amendment dated 8/13/01 in paper no. 27 amends the specification (e.g. on pages 19-20) to recite "Serial No 144,964" without specifying the application series (e.g. 09/).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (NEW MATTER REJECTION).

Amending claims 33 and 34 to change the libraries to encompass N-terminal peptide and C-terminal peptide segments derived from different **families** of parent proteins instead of different parent proteins constitutes new matter; e.g. neither supported in the specification nor does applicant indicate where such support is present. Applicant must cancel the new matter in response to this rejection.

7. Claims 28-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (INADEQUATE WRITTEN DESCRIPTION REJECTION).

The specification fails to provide sufficient written description to support a genus of cross-over proteins which are devoid of sequence length, amino acid content, specific biological function which is produced by the presently claimed method of ligating one or more peptide

segments derived from one or more first protein(s) and one or more second protein(s) whether of the same or different family or classes. There is a limited showing of ligating protein fragments from the same "class" of protein (e.g. chemokines: such as RANTES etc.) but no examples regarding the ligation of peptide fragments from different classes. Different classes of compounds would lack a common core structure which elicits a common activity and would broadly encompass both functionally and structurally distinct peptides including hormones, enzymes etc.

In this regard, applicant is referred to the seminal case of *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and the resulting "Guidelines for Examination of Patent Applications Under the 35 USC 112, first paragraph, 'Written Description' Requirement" published in 1242 OG 168-178 (January 30, 2001).

It is first noted that written description is legally distinct from enablement: "Although the two concepts of are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures the that the inventor conveys to others that he or she had possession of the claimed invention; whereas, the enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co*

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by

structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

However, it is clear that applicant has not presented an adequate sample to demonstrate possession of the presently claimed invention. See *University of California v. Eli Lilly and Co.* U.S. Court of Appeals Federal Circuit (CA FC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997 No. 96-1175 regarding adequate disclosure, the analysis of which does not address the absence or presence of undue experimentation.

For the specification discloses only limited examples that are neither representative of the claimed genus (which is not limited by peptide length or amino acid composition nor types of derivations), nor is it clear that they represent a substantial portion of the claimed genus. This showing clearly does not provide an adequate representation regarding the myriad possible cross-over proteins or peptides of different length which lack a common core which would be expected to elicit a common activity.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 28-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 28, line 9, "said first *parent* protein" lacks clear antecedent basis.

B. In claims 28 and 32 (and claims dependent thereon), the use of the terms "N-terminal peptide segment" and "C-terminal peptide segment" is indefinite for the following reasons: it is unclear what "N--terminal" and "C-terminal" is referring to:

I. Is it referring to the N-terminal peptide segment of the protein from which it is derived (e.g. "First" or "Second" protein);

II. Is it referring to the position of the segments in the ultimate cross-over protein e.g. the N-terminal segment is the first half and the C-terminal segment is the second half of the ultimate cross-over protein.

Additionally, it is further confusing when there are more than one N-terminal peptide or C-terminal segment as to how the terms "N-terminal" and "C-terminal" peptide segments are descriptive of either derivation (as in I. above) or position (as in II. above).

Additionally, use of the N-terminal peptide segment" and "C-terminal peptide segment" is further confusing since the N-terminus and C-terminus of a peptide or protein is understood in the art to refer to a single amino acid and not a segment of amino acids.

Further, the terms "N-terminal and C-terminal peptide segments" in the claims are relative terms which renders the claim indefinite. These terms are not defined by the claim, nor does the

specification provide a standard for ascertaining the requisite degree (e.g. how many amino acids in a peptide/protein encompass an N-terminal or C-terminal segment), and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, in a 1500 amino acid protein (e.g. numbered 1-1500) what number of amino acids constitute an N-terminal peptide segment (e.g. 1, 2, 5, 50, 100, 700 ???????????"?).

C. In claims 30, 33-35 (and claims dependent thereon) the terms "same (different) *family* of protein molecules" are relative terms which renders the claims indefinite. The term "family of protein molecules" is not defined by the claim, nor does the specification provide a standard for ascertaining the requisite degree of relatedness (structure, function , conformation etc.) of various proteins to be classifiable as being from the same or different families, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Additionally, neither the specification nor claims indicate what characteristics (e.g. chemical, structure, conformational etc) distinguishes one "family" of proteins from another.

D. In claims 28 and 32 (last line) use of the term "having a C-terminus and an N-terminus" is redundant and additionally confusing in light of the use of analogous language regarding peptide segments.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

11. Claims 28-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Canne et al., JACS Vol. 117 (1995) pages 2998-3007.

Canne et al. disclose a chemical ligation chemoselective method of making both **hetero-** and homo- **dimers** utilizing a "***modular strategy***" (abstract) (emphasis provided). The Canne et al. method extends the native peptide ligation (e.g. see page 2999, beginning of left paragraph and citation no. 13 to Science article: herein the "Science article") chemoselective technique to other ligation chemistries (e.g. thioesters, oximes, hydrazones, disulfides, thiazolidones etc.: see page 2999 left column) and to the formation of "complex protein analogues" (not just single protein syntheses as described in the Science article) which would allow for the condensation of more than two (e.g. "Three or more") unprotected **peptide segments** in a specific manner utilizing chemical ligation (emphasis provided). Accordingly, the Canne et al. Reference suggests the use of chemoselective chemical ligation to condense two or more peptide segments once or in a multiple manner using the native chemical ligation strategy (e.g. in the Science article) and/or different chemoselective ligation chemistries. The Canne reference further teaches the use of chemoselective chemical ligation (e.g. including native chemical ligation) in a modular strategy to

generate heterodimers utilizing two or more fragments of transcriptional regulatory proteins (e.g. cMyc and Max) that comprise protein domains (e.g. see schemes and figures especially schemes 1 and 3). Accordingly, the Canne et al. Reference method discloses the use of reactants (e.g. peptide segments derived from different proteins which comprise different functional domains e.g. "functional protein module(s)") which are chemoselectively ligated to form "cross over proteins" within the scope of the presently claimed inventions. It is noted that the reference explicitly teaches the ligation of peptide fragments which contain "reactive groups" (e.g. derived carboxyl terminus) that form the "cross over protein" within the scope of the presently claimed invention (e.g. the presently claimed invention is *not limited to head-to-tail covalent linkage as argued by applicant*).

12. Claims 28-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Clark-Lewis et al., J. Biol. Chem. Vol. 269 No. 23 (6/94) pages 16075-16081..

The Clark-Lewis reference discloses the formation of cross over proteins which comprise fragments from two different proteins (e.g. IL-8 and IL-10 e.g. in the same family) each fragment having reactive groups (e.g. SH's) which results in chemical ligation (e.g. disulfide linkage) e.g. see page 16079-16080 and hybrids disclosed therein. The ligated IL-8 and IL-10 comprised "Functional Protein Modules" within the presently claimed invention (e.g. see specification definition at page 7) since in the reference, "protein folding" (e.g. beta turns) correlates with "a particular functionality" (e.g. function as measured by potency and elastase release) in a sequence

specific manner (e.g. differed from reference hybrids IP10H-1 - IP10H-8) It is noted that the Clarke-Lewis reference explicitly teaches the ligation of peptide fragments (e.g. disulfide linkage) which contain "reactive groups" (e.g. Cys amino acids with SH side chains) that form the "cross over protein" within the scope of the presently claimed invention (e.g. the presently claimed invention is *not limited to head-to-tail covalent linkage as argued by applicant*).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 28-31 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Canne et al., JACS Vol. 117 (1995) pages 2998-3007 and Dawson et al. Science Vol. 266 (11/94) pages 776-779 specifically cited in the Canne et al. Reference at page 6588 footnote (13).

Canne et al. disclose a chemical ligation chemoselective method of making both **hetero-** and homo- **dimers** utilizing a "***modular strategy***" (abstract) (emphasis provided). The Canne et al. method extends the native peptide ligation (e.g. see page 2999, beginning of left paragraph and citation no. 13 to Science article: herein the "Science article") chemoselective technique to other ligation chemistries (e.g. thioesters, oximes, hydrazones, disulfides, thiazolidones etc.: see page 2999 left column) and to the formation of "complex protein analogues" (not just single protein syntheses as described in the Science article) which would allow for the condensation or more than two (e.g. "Three or more") unprotected **peptide segments** in a specific manner utilizing chemical ligation (emphasis provided). Accordingly, the Canne et al. Reference suggests the use of chemoselective chemical ligation to condense two or more peptide segments once or in a multiple manner using the native chemical ligation strategy (e.g. in the Science article) and/or different chemoselective ligation chemistries. The Canne reference further teaches the use of chemoselective chemical ligation (e.g. including native chemical ligation) in a modular strategy to generate heterodimers utilizing two or more fragments of transcriptional regulatory proteins (e.g. cMyc and Max) that comprise protein domains (e.g. see schemes and figures especially schemes 1 and 3). Accordingly, the Canne et al. Reference method discloses the use of reactants (e.g.

peptide segments derived from different proteins which comprise different functional domains e.g. "functional protein module(s)") which are chemoselectively ligated to form "cross over proteins" within the scope of the presently claimed inventions. It is noted that the reference explicitly teaches the ligation of peptide fragments which contain "reactive groups" (e.g. derived carboxyl terminus) that form the "cross over protein" within the scope of the presently claimed invention (e.g. the presently claimed invention is *not limited to head-to-tail covalent linkage as argued by applicant*)

To the extent that the presently claimed invention encompasses head to tail ligation (amino terminal amino acid of a fragment to carboxl terminal of a different fragment) to form a cross over protein it is noted that the Canne et al. reference specifically recites the application of a small number of types of chemical ligation techniques which preferably include the Science article native chemical ligation approach (e.g. see Science article page 777 Fig. 1) which illustrates head-to-tail covalent ligation. Accordingly, the Canne reference incorporation of the Science reference article describing the native chemical ligation approach (e.g. head to tail ligation) would render its selection from such a limited number of ligation techniques either immediately envisaged (e.g anticipated) or alternatively obvious to one of ordinary skill in the art at the time of applicant's invention. E.g. See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978).

15. Claims 28-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Canne et al., JACS Vol. 117 (1995) pages 2998-3007, Dawson et al. Science Vol. 266 (11/94) pages 776-779 and Pavia eta l., Biorg. & Medicinal Chem. Lett. Vol. 3, No. 3 pages 387-396.

Canne et al. disclose a chemical ligation chemoselective method of making both **hetero-** and homo- **dimers** utilizing a "***modular strategy***" (abstract) (emphasis provided). The Canne et al. method extends the native peptide ligation (e.g. see page 2999, beginning of left paragraph and citation no. 13 to Science article: herein the "Science article") chemoselective technique to other ligation chemistries (e.g. thioesters, oximes, hydrazones, disulfides, thiazolidones etc.: see page 2999 left column) and to the formation of "complex protein analogues" (not just single protein syntheses as described in the Science article) which would allow for the condensation or more than two (e.g. "Three or more") unprotected **peptide segments** in a specific manner utilizing chemical ligation (emphasis provided). Accordingly, the Canne et al. Reference suggests the use of chemoselective chemical ligation to condense two or more peptide segments one or in a multiple manner using the native chemical ligation strategy (e.g. in the Science article) and/or different chemoselective ligation chemistries. The Canne reference further teaches the use of chemoselective chemical ligation (e.g. including native chemical ligation) in a modular strategy to generate heterodimers utilizing two or more fragments of transcriptional regulatory proteins (e.g. cMyc and Max) that comprise protein domains (e.g. see schemes and figures especially schemes 1 and 3). Accordingly, the Canne et al. Reference method discloses the use of reactants (e.g. peptide segments derived from different proteins which comprise different functional domains

e.g. "functional protein module(s)") which are chemoselectively ligated to form "cross over proteins" within the scope of the presently claimed inventions. It is noted that the reference explicitly teaches the ligation of peptide fragments which contain "reactive groups" (e.g. derived carboxyl terminus) that form the "cross over protein" within the scope of the presently claimed invention (e.g. the presently claimed invention is *not limited to head-to-tail covalent linkage as argued by applicant*)

To the extent that the presently claimed invention encompasses head to tail ligation (amino terminal amino acid of a fragment to to carboxyl terminal of a different fragment) to form a cross over protein the Canne et al. reference specifically recites the application of a small number of types of chemical ligation techniques which preferably include the Science article native chemical ligation approach (e.g. see Science article page 777 Fig. 1) which illustrates head-to-tail covalent ligation. Accordingly, the Canne reference incorporation of the Science reference article describing the native chemical ligation approach (e.g. head to tail ligation) would render its selection from such a limited number of ligation techniques either immediately envisage (e.g anticipation) or alternatively obvious to one of ordinary skill in the art at the time of applicant's invention. E.g. See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978).

The Canne et al. Reference teaching taken alone, or in conjunction with the teaching of the Science reference, teaches the making of prospective analogues (e.g. ligands) by chemical ligation of peptide fragments one at a time for biological evaluation which differs from the presently

claimed invention (e.g. claims 32-36) which is drawn to the making and screening of libraries of ligands for biological evaluation.

However, the Pavia et al. reference teaches that the traditional serial process of synthesizing and testing peptide analogues one at a time is being replaced by the use of combinatorial library syntheses strategies since the libraries provide the ability to increase molecular diversity and utilize high throughput screening which optimizes drug discovery See e.g. Pavia et al. Abstract; page 391 ("Automated Methods").

Accordingly, one of ordinary skill in the art would be motivated to generate libraries of compounds by utilization of the Canne reference modular strategy in order to optimize drug discovery.

Thus, modification of the Canne reference method alone or in view of the Science reference ligation technique to utilize combinatorial libraries would have been obvious to one of ordinary skill in the art at the time of applicant's invention in order to optimize drug discovery.

16. Claims 28-30 and 32-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clark-Lewis et al., J. Biol. Chem. Vol. 269 No. 23 (6/94) pages 16075-16081 and Pavia et al., Biorg. & Medicinal Chem. Lett. Vol. 3, No. 3 pages 387-396.

The Clark-Lewis reference discloses the formation of cross over proteins which comprise fragments from two different proteins (e.g. IL-8 and IL-10 e.g. in the same family) each fragment having reactive groups (e.g. SH's) which results in chemical ligations (e.g. disulfide linkage) chemically ligated (e.g. see page 16079-16080 and hybrids disclosed therein). The ligated IL-8 and IL-10 comprised "Functional Protein Modules" within the presently claimed invention (e.g. see specification definition at page 7) since "protein folding" (e.g. beta turns) correlated with "a particular functionality" (e.g. function as measured by potency and elastase release) in a sequence specific manner (e.g. differed from reference hybrids IP10H-1 - IP10H-8) It is noted that the Clarke-Lewis reference explicitly teaches the ligation of peptide fragments (e.g. disulfide linkage) which contain "reactive groups" (e.g. Cys amino acids with SH side chains) that form the "cross over protein" within the scope of the presently claimed invention (e.g. the presently claimed invention is *not limited to head-to-tail covalent linkage as argued by applicant*).

The Clarke-Lewis reference teaching of making prospective analogues (e.g. ligands) by chemical ligation of peptide fragments one at a time for biological evaluation differs from the presently claimed invention (e.g. claims 32-35) which is drawn to the making and screening of libraries of ligands for biological evaluation.

However, the Pavia et al. reference teaches that the traditional serial process of synthesizing and testing peptide analogues one at a time is being replaced by the use of combinatorial library syntheses strategies since the libraries provide the ability to increase molecular diversity and utilize high throughput screening which optimizes drug discovery See e.g. Pavia et al. Abstract; page 391 ("Automated Methods").

Accordingly, one of ordinary skill in the art would be motivated to generate libraries of compounds by utilization of the Clarke-Lewis reference method in order to optimize drug discovery.

Thus, modification of the Clarke-Lewis reference method technique to utilize combinatorial libraries would have been obvious to one of ordinary skill in the art at the time of applicant's invention in order to optimize drug discovery.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 28-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims (e.g. claims 1-7) of U.S. Patent No. 6,184,344 in view of Canne et al., JACS Vol. 117 (1995) pages 2998-3007.

The Patent claims teach native chemical ligation approach (e.g. head to tail ligation) of a first and second oligopeptide.

The patent claims fail to teach the use of oligopeptide fragments from different proteins (e.g. comprising a functional protein module) to form a cross-over (e.g hybrid) proteins .

However, the Canne et al. Reference disclose a chemical ligation chemoselective method of making both **hetero-** and homo- **dimers** utilizing a "***modular strategy***" (abstract) (emphasis provided). The Canne et al. method extends the native peptide ligation (e.g. see page 2999, beginning of left paragraph and citation no. 13 to Science article: herein the "Science article") (which is synonymous with the patented claim method) chemoselective technique to other ligation

chemistries (e.g. thioesters, oximes, hydrazones, disulfides, thiazolidones etc.: see page 2999 left column) and to the formation of "complex protein analogues" (not just single protein syntheses as described in the Science article) which would allow for the condensation or more than two (e.g. "Three or more") unprotected **peptide segments** in a specific manner utilizing chemical ligation (emphasis provided). Accordingly, the Canne et al. Reference suggests the use of chemoselective chemical ligation to condense two or more peptide segments once or in a multiple manner using the native chemical ligation strategy (e.g. in the Science article) and/or different chemoselective ligation chemistries.

Accordingly, the Canne reference teaching of the use of chemoselective chemical ligation (e.g. including native chemical ligation) in a modular strategy to generate heterodimers utilizing two or more fragments of transcriptional regulatory proteins (e.g. cMyc and Max) that comprise protein domains (e.g. see schemes and figures especially schemes 1 and 3) would motivate one of ordinary skill in the art to utilize the patented claim process in the Canne modular strategy and thus render obvious the presently claimed invention..

19. Claims 32-36 are rejected under 35 U.S.C. 103(a) as being rejected for obviousness-type double patenting over U.S. Patent No. 6,184,344 in view of Canne et al., JACS Vol. 117 (1995) pages 2998-3007 as applied to claims 28-31 above, and further in view of Pavia et al., Biorg. & Medicinal Chem. Lett. Vol. 3, No. 3 pages 387-396.

The '344 and Canne et al. combined teaching of making prospective analogues (e.g. ligands) by chemical ligation of peptide fragments one at a time for biological evaluation differs

from the presently claimed invention (e.g. claims 32-36) which is drawn to the making and screening of libraries of ligands for biological evaluation.

However, the Pavia et al. reference teaches that the traditional serial process of synthesizing and testing peptide analogues one at a time is being replaced by the use of combinatorial library syntheses strategies since the libraries provide the ability to increase molecular diversity and utilize high throughput screening which optimizes drug discovery See e.g. Pavia et al. Abstract; page 391 ("Automated Methods").

Accordingly, one of ordinary skill in the art would be motivated to generate libraries of compounds by utilization of the '344 and Canne et al. reference method in order to optimize drug discovery.

Thus, modification of the '344 and Canne et al. reference method technique to utilize combinatorial libraries would have been obvious to one of ordinary skill in the art at the time of applicant's invention in order to optimize drug discovery.

20. Claims 28-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims (e.g. claims 1-7) of U.S. Patent No. 6,326,468 in view of Canne et al., JACS Vol. 117 (1995) pages 2998-3007.

The Patent claims teach native chemical ligation approach (e.g. head to tail ligation) of a first and second oligopeptide.

The patent claims fail to teach the use of oligopeptide fragments from different proteins (e.g. comprising a functional protein module) to form a cross-over (e.g hybrid) protein .

However, the Canne et al. Reference disclose a chemical ligation chemoselective method of making both **hetero-** and homo- **dimers** utilizing a "***modular strategy***" (abstract) (emphasis provided). The Canne et al. method extends the native peptide ligation (e.g. see page 2999, beginning of left paragraph and citation no. 13 to Science article: herein the "Science article") (which is synonymous with the patented claim method) chemoselective technique to other ligation chemistries (e.g. thioesters, oximes, hydrazones, disulfides, thiazolidones etc.: see page 2999 left column) and to the formation of "complex protein analogues" (not just single protein syntheses as described in the Science article) which would allow for the condensation or more than two (e.g. "Three or more") unprotected **peptide segments** in a specific manner utilizing chemical ligation (emphasis provided). Accordingly, the Canne et al. Reference suggests the use of chemoselective chemical ligation to condense two or more peptide segments one or in a multiple manner using the native chemical ligation strategy (e.g. in the Science article) and/or different chemoselective ligation chemistries.

Accordingly, the Canne reference teaching of the use of chemoselective chemical ligation (e.g. including native chemical ligation) in a modular strategy to generate heterodimers utilizing two or more fragments of transcriptional regulatory proteins (e.g. cMyc and Max) that comprise protein domains (e.g. see schemes and figures especially schemes 1 and 3) would motivate one of ordinary skill in the art to utilize the patented claim process in the Canne modular strategy and thus render obvious the presently claimed invention..

21. Claims 32-36 are rejected under 35 U.S.C. 103(a) as being rejected for obviousness-type double patenting over U.S. Patent No 6,326,468 in view of Canne et al., JACS Vol. 117 (1995) pages 2998-3007 as applied to claims 28-31 above, and further in view of Pavia et al., Biorg. & Medicinal Chem. Lett. Vol. 3, No. 3 pages 387-396.

The '468 and Canne et al. combined teaching of making prospective analogues (e.g. ligands) by chemical ligation of peptide fragments one at a time for biological evaluation differs from the presently claimed invention (e.g. claims 32-36) which is drawn to the making and screening of libraries of ligands for biological evaluation.

However, the Pavia et al. reference teaches that the traditional serial process of synthesizing and testing peptide analogues one at a time is being replaced by the use of combinatorial library syntheses strategies since the libraries provide the ability to increase molecular diversity and utilize high throughput screening which optimizes drug discovery See e.g. Pavia et al. Abstract; page 391 ("Automated Methods").

Accordingly, one of ordinary skill in the art would be motivated to generate libraries of compounds by utilization of the '468 and Canne et al. reference method in order to optimize drug discovery.

Thus, modification of the '468 and Canne et al. reference method technique to utilize combinatorial libraries would have been obvious to one of ordinary skill in the art at the time of applicant's invention in order to optimize drug discovery.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat (art unit 1627), can be reached at (703)308-0570.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1627)

November 27, 2001

BENNETT CELSA
PRIMARY EXAMINER